Biol Blood Marrow Transplant 21 (2015) 1776–1782

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Tacrolimus versus Cyclosporine after Hematopoietic Cell Transplantation for Acquired Aplastic Anemia

Yoshihiro Inamoto [1,*], Mary E.D. Flowers [2], Tao Wang [3,4], Alvaro Urbano-Ispizua [5], Michael T. Hemmer [3], Corey S. Cutler [6], Daniel R. Couriel [7], Amin M. Alousi [8], Joseph H. Antin [6], Robert Peter Gale [9], Vikas Gupta [10], Betty K. Hamilton [11], Mohamed A. Kharfan-Dabaja [12], David I. Marks [13], Olle T.H. Ringdén [14,15], Gérard Socié [16], Melhem M. Solh [17], Görgün Akpek [18], Mitchell S. Cairo [19], Nelson J. Chao [20], Robert J. Hayashi [21], Taiga Nishihori [12], Ran Reshef [22], Ayman Saad [23], Ami Shah [24], Takanori Teshima [25], Martin S. Tallman [26], Baldeep Wirk [27], Stephen R. Spellman [28], Mukta Arora [29], Paul J. Martin [2]

[1] *Division of Hematopoietic Stem Cell Transplantation, National Cancer Center Hospital, Tokyo, Japan*
[2] *Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington*
[3] *Center for International Blood and Marrow Transplant Research, Department of Medicine, Medical College of Wisconsin, Milwaukee, Wisconsin*
[4] *Division of Biostatistics, Institute for Health and Society, Medical College of Wisconsin, Milwaukee, Wisconsin*
[5] *Department of Hematology, Hospital Clinic, University of Barcelona, IDIBAPS and Institute of Research Josep Carreras, Barcelona, Spain*
[6] *Center for Hematologic Oncology, Department of Medical Oncology, Dana-Farber Cancer Institute, Boston, Massachusetts*
[7] *Department of Medicine, University of Michigan, Ann Arbor, Michigan*
[8] *Division of Cancer Medicine, Department of Stem Cell Transplantation, University of Texas M.D. Anderson Cancer Center, Houston, Texas*
[9] *Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College of London, London, United Kingdom*
[10] *Blood and Marrow Transplant Program, Princess Margaret Cancer Centre, University Health Network, Toronto, Ontario, Canada*
[11] *Blood and Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio*
[12] *Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, Florida*
[13] *Pediatric Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom*
[14] *Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden*
[15] *Centre for Allogeneic Stem Cell Transplantation, Stockholm, Sweden*
[16] *Department of Hematology, Hospital Saint Louis, Paris, France*
[17] *Blood and Marrow Transplant Center, Florida Hospital Medical Group, Orlando, Florida*
[18] *Stem Cell Transplantation and Cellular Therapy Program, Banner MD Anderson Cancer Center, Gilbert, Arizona*
[19] *Department of Pediatrics, New York Medical College, Valhalla, New York*
[20] *Division of Cell Therapy and Hematologica, Department of Medicine, Duke University Medical Center, Durham, North Carolina*
[21] *Division of Pediatric Hematology/Oncology, Department of Pediatrics, Washington University School of Medicine in St. Louis, St. Louis, Missouri*
[22] *Department of Medicine, Abramson Cancer Center, University of Pennsylvania Medical Center, Philadelphia, Pennsylvania*
[23] *Division of Hematology/Oncology, Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama*
[24] *Division of Hematology/Oncology, Department of Pediatrics, Mattel Children's Hospital at University of California Los Angeles, Los Angeles, California*
[25] *Department of Hematology, Hokkaido University Graduate School of Medicine, Sapporo, Japan*
[26] *Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, New York*
[27] *Division of Bone Marrow Transplant, Seattle Cancer Care Alliance, Seattle, Washington*
[28] *Center for International Blood and Marrow Transplant Research, National Marrow Donor Program/Be The Match, Minneapolis, Minneapolis*
[29] *Division of Hematology, Oncology, Transplantation, Department of Medicine, University of Minnesota Medical Center, Minneapolis, Minnesota*

Article history:
Received 25 March 2015
Accepted 23 May 2015

Key Words:
Aplastic anemia
Hematopoietic cell transplantation
Graft-versus-host disease
Immunosuppression

A B S T R A C T

Combinations of cyclosporine (CSP) with methotrexate (MTX) have been widely used for immunosuppression after allogeneic transplantation for acquired aplastic anemia. We compared outcomes with tacrolimus (TAC)+MTX versus CSP+MTX after transplantation from HLA-identical siblings (SIB) or unrelated donors (URD) in a retrospective cohort of 949 patients with severe aplastic anemia. Study endpoints included hematopoietic recovery, graft failure, acute graft-versus-host disease (GVHD), chronic GVHD, and mortality. TAC+MTX was used more frequently in older patients and, in recent years, in both SIB and URD groups. In multivariate analysis, TAC+MTX was associated with a lower risk of mortality in URD recipients and with slightly earlier absolute neutrophil count recovery in SIB recipients. Other outcomes did not differ statistically

Financial disclosure: See Acknowledgments on page 1781.
* Correspondence and reprint requests: Yoshihiro Inamoto, MD, National Cancer Center Hospital, 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan.
E-mail address: yinamoto@ncc.go.jp (Y. Inamoto).

http://dx.doi.org/10.1016/j.bbmt.2015.05.023

Cyclosporine
Tacrolimus

between the 2 regimens. No firm conclusions were reached regarding the relative merits of TAC+MTX versus CSP+MTX after hematopoietic cell transplantation for acquired aplastic anemia. Prospective studies would be needed to determine whether the use of TAC+MTX is associated with lower risk of mortality in URD recipients with acquired aplastic anemia.

INTRODUCTION

Allogeneic hematopoietic cell transplantation (HCT) is a curative treatment for patients with severe aplastic anemia (SAA), but graft failure and graft-versus-host disease (GVHD) have impeded its success [1-8]. Combinations of cyclosporine (CSP) or tacrolimus (TAC) with methotrexate (MTX) have been widely used for immunosuppression after allogeneic HCT [2,9-13]. CSP has been used preferentially after HCT for SAA [14] whereas TAC has been used preferentially after HCT for hematological malignancies, since 3 prospective randomized studies of bone marrow transplantation (BMT) showed lower risks of acute and chronic GVHD with TAC more than a decade ago [9-11].

Outcomes with TAC+MTX versus CSP+MTX after unrelated BMT for patients with SAA have been compared in only 1 Japanese study [15]. In a matched-pair retrospective study of 94 patients, the risk of mortality was lower with the use of TAC+MTX [15], but rates of acute and chronic GVHD did not differ statistically between the 2 prophylaxis regimens. These results have not been validated in larger cohorts with related or unrelated donors or evaluated in patients who received growth factor–mobilized peripheral blood cell transplantation (PBSCT). The purpose of the current study was to compare outcomes with TAC+MTX versus CSP+MTX after HCT for SAA using data collected by the Center for International Bone Marrow Transplant Research (CIBMTR). As observed in several studies mostly including patients with hematological malignancies [9-12,16], we anticipated that TAC+MTX would be associated with lower risks of acute and chronic GVHD after HCT for SAA.

METHODS

Patients

This retrospective study cohort included patients reported to the CIBMTR who had their first allogeneic BMT or PBSCT from HLA-identical siblings (SIB) or from unrelated donors (URD) for treatment of acquired SAA from January 2001 to December 2011. Patients who had GVHD prophylaxis other than CSP+MTX or TAC+MTX, those who received ex vivo T cell–depleted grafts, and those with congenital disorders were excluded, leaving 949 eligible patients in the cohort. CIBMTR observational studies using deidentified data comply with Health Insurance Portability and Accountability Act regulations and are conducted with a waiver of informed consent per the institutional review board of the Medical College of Wisconsin.

Study Endpoints and Definitions

Study endpoints included hematopoietic recovery, secondary graft failure, grades II to IV acute GVHD, grades III and IV acute GVHD, limited or extensive chronic GVHD, and mortality. *Time to neutrophil* and *platelet recovery* were defined as the time from transplantation to the first of 3 consecutive days with an absolute neutrophil count (ANC) $\geq 500/mm^3$ and platelet count $\geq 20 \times 10^9$/L unsupported by transfusion for 7 days, respectively. *Secondary graft failure* was defined as subsequent loss of ANC to $< 500/mm^3$ and $< 5\%$ donor chimerism after neutrophil recovery. Acute GVHD was graded according to consensus criteria [17]. Chronic GVHD was diagnosed by historical criteria [18]. HLA matching was defined as described previously [19].

Statistical Analysis

Multivariate Cox regression models were constructed to evaluate hazard ratios (HR) for endpoints with TAC+MTX compared with CSP+MTX. Factors violating the proportional hazards assumption were adjusted through stratification. A stepwise procedure was used in developing models for each outcome, using a P value threshold of .05. All models were adjusted for graft type (BMT versus PBSCT) and year of transplantation. Center effect was also adjusted as a random effect to account for differences in practice at individual centers, including the choice and targeted blood concentrations of calcineurin inhibitors [20]. Analyses were performed separately in SIB and URD recipients. Interactions between the main variable (GVHD prophylaxis) and the adjusted covariates were tested at the significance level of .01. Proportions of causes of death were compared using Fisher's exact test.

RESULTS

Transplantation from an HLA-identical Donor

Patient characteristics are summarized in Table 1. SIB recipients who received TAC+MTX were older and more frequently of Caucasian race, had older donors, had more frequent treatment for SAA with antithymocyte globulin (ATG) before HCT, had HCT in more recent years with more frequent use of cyclophosphamide-based conditioning, ATG or alemtuzumab, and hematopoietic growth factors after HCT. In multivariate analysis (Figure 1A), TAC+MTX was associated only with earlier ANC recovery (HR, 1.47; 95% confidence interval, 1.04 to 2.08; $P = .03$). Other outcomes did not differ statistically between the 2 regimens. No statistically significant interactions were observed between the main variable and the adjusted covariates. The proportion of graft failure as a cause of death was higher with TAC+MTX than with CSP+MTX (overall $P = .007$; Table 2).

Transplantation from an URD

URD recipients who received TAC+MTX were older and less frequently of Caucasian race, had younger donors, had HCT in more recent years with more frequent use of cyclophosphamide-based conditioning including total body irradiation with less frequent use of ATG or alemtuzumab, and more frequent use of PBSCT and hematopoietic growth factors after HCT (Table 1). In multivariate analysis (Figure 1B), TAC+MTX was associated with a lower risk of mortality (HR, .42; 95% confidence interval, .23 to .80; $P = .008$). Other outcomes did not differ statistically between the 2 regimens. No statistically significant interactions were observed between the main variable and the adjusted covariates. Causes of death were similar between the 2 GVHD prophylaxis regimens (overall $P = .91$) (Table 2). Because several studies showed inferior survival after PBSCT compared with after BMT for SAA [21-24], stratified analysis was also performed by graft type (Figure 2). Results for BMT were similar to results of the nonstratified analysis. Results for PBSCT showed no statistically significant differences for any outcome, but analytic power was limited in this subgroup.

DISCUSSION

In the absence of a prospective, randomized comparison, this large international cohort study provides valuable information. Based on adjusted multivariate analyses, the use of TAC+MTX was unexpectedly associated with a lower risk of mortality among URD recipients and with slightly